

Original Article

Posterior sub-tenon's bevacizumab injection in diabetic macular edema; a pilot study



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Abstract

Purpose: To evaluate the short-term results of sub-tenon's injection of bevacizumab in patients with clinically significant macular edema (CSME).

Methods: In this prospective non-comparative interventional case series, sub-tenon's injection of 2.5 mg/0.1 ml bevacizumab was performed for eyes with CSME. Macular thickness and best corrected visual acuity measurements were performed before and one month after injections.

Results: Nineteen eyes of twelve patients with a mean age of 59.8 ± 5.7 years were evaluated. Thirteen eyes (68.4%) had center-involving macular edema. No significant difference was observed between pre- and post-injection central subfield retinal thickness measurements ($P = 0.3$). Central subfield thickness measurements improved or remained unchanged in 13 eyes (68.4%). Baseline BCVA of 0.48 ± 0.35 LogMAR improved to 0.36 ± 0.26 LogMAR after injection ($P = 0.01$). Improvement of >2 lines in BCVA was found in 5 eyes (26.3%), and no eye lost >2 lines of BCVA. No complication associated with sub-tenon's injection was observed.

Conclusion: Sub-tenon's injection of bevacizumab resulted in significant short-term visual improvement in eyes with CSME. Retinal thickness changes were not significant.

Keywords: Bevacizumab, Diabetic retinopathy, Macular edema, Sub-tenon's injection

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Introduction

Macular edema is one of the main causes of visual impairment in patients with diabetic retinopathy.¹ The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that macular photocoagulation reduced the risk of moderate visual acuity loss in eyes with clinically significant macular edema (CSME) by approximately 50%.² The aim of the macular photocoagulation treatment in CSME is to prevent further visual loss and improvement of visual acuity occurs in about 10–20% of eyes.^{2–4} Treatment of diabetic macular edema with anti-vascular

endothelial growth factor (VEGF) agents has resulted in superior outcomes compared to conventional laser photocoagulation. Currently, the treatment of choice for diffuse diabetic macular edema is intravitreal injection of anti-VEGF agents alone or in combination with laser photocoagulation.^{5,6}

Although previous studies have shown the efficacy of intravitreal anti-VEGF injections in various retinal diseases, each intravitreal injection poses the risk of post-injection ocular adverse events including infectious endophthalmitis, intraocular inflammation, intraocular pressure elevation and retinal detachment.⁷

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Diffusion through the sclera is a known method for the delivery of various medications into the eye.⁸ Promising results have been reported with sub-tenon's injection of triamcinolone for the treatment of diabetic macular edema.^{9,10} Liang et al.¹¹ reported successful treatment of myopic choroidal neovascularization (CNV) with posterior sub-tenon's bevacizumab (STB) injection. To our knowledge, no other study has reported the use of sub-tenon's injection of anti-VEGF agents in ocular diseases. The aim of this pilot study was to evaluate the results of STB injections in eyes with CSME. If found useful, the STB is a less invasive alternative for the treatment of diabetic macular edema as compared to intravitreal injections.

Methods

In this prospective non-comparative interventional case series, from January to May 2014, all patients with clinically significant diabetic macular edema (according to EDTRS classification)² who underwent STB injection were included. We considered STB injection for eyes with non-center involved macular edema who were candidate for macular photocoagulation.^{3,4} Patients with center involving macular edema who were eligible for intravitreal anti-VEGF therapy but rejected the intravitreal injections due to the possible complications associated with intravitreal injections, were also considered for STB treatment. Macular photocoagulation was performed for all patients one month after STB injections. The study protocol was approved by the Rassoul Akram Hospital Eye Research Center Ethics Committee and informed consents were obtained.

Exclusion criteria were the history of intraocular surgery during last 8 months, history of retinal laser photocoagulation, high refractive errors (>6 diopters of sphere or >3 diopters of cylinder), media opacity affecting visual acuity and optical coherence tomography (OCT) measurements, history of glaucoma or intraocular pressure more than 22 mmHg, ischemic or inflammatory optic neuropathy, uveitis, retinal vascular occlusion, vitreomacular interface disorders and the need for panretinal photocoagulation. Both eyes of each participant were enrolled if both eyes met the inclusion criteria.

Complete ophthalmic examination including best corrected visual acuity measurement (BCVA) using a standard Snellen chart (converted to LogMAR), and slit lamp and dilated fundus examination was performed. Macular thickness measurements were taken with a 3D spectral domain OCT-1000 device (software version 3.32.003.04, Topcon Incorporation, Tokyo, Japan). A 3D Scan 512 × 128 protocol, covering a 6 × 6 mm² centered on the fovea was used for all measurements. Images with inadequate quality factor (<45), discontinuity, misalignment, involuntary saccade or blinking artifacts were excluded. OCT imaging and BCVA measurements were taken immediately before and one month after STB injections.

All injections were performed in the office. After instillation of a drop of tetracaine, one drop of 5% povidone-iodine was instilled in the fornix. The lids were kept open by the surgeon and no speculum was used. The patients were asked to look at the contralateral shoulder. The injections were performed into the sub-tenon's space in the superotemporal fornix (as far posteriorly as could be easily visualized, nearly

more than 8 mm from limbus) with a 27-gauge needle under direct visualization. Each injection consisted of 2.5 mg bevacizumab in 0.1 mm volume.

Statistical analyses were performed with a SPSS software (version 15, SPSS Inc. Chicago, IL) and paired t test and correlation test were used for analysis. $P < 0.05$ was considered significant. The average retinal thickness in central 1 mm and 3 mm of the OCT macular grid was considered central subfield thickness (CST) and central macular thickness (CMT), respectively. Considering the intersession repeatability of the OCT instrument, CST changes >14.5 μm were considered clinically significant.¹²

Results

Nineteen eyes of twelve patients including 5 men and 7 women with a mean age of 59.8 ± 5.7 years were assessed. Thirteen eyes (68.4%) had center-involving macular edema.

Central subfield retinal thickness was $350.7 \pm 113.3 \mu\text{m}$ and $337.6 \pm 109.7 \mu\text{m}$ before and one month after injections, respectively ($P = 0.3$). Mean change in CST was $-13.1 \pm 61.5 \mu\text{m}$. Seven eyes (36.8%) had a clinically significant decrease in CST and a clinically significant increase in CST was observed in 6 eyes (31.5%). Central macular thickness was $362.4 \pm 68.7 \mu\text{m}$ and $355.4 \pm 63.5 \mu\text{m}$ before and after injections, respectively ($P = 0.2$).

Baseline BCVA of 0.48 ± 0.35 LogMAR improved to 0.36 ± 0.26 LogMAR after injection ($P = 0.01$). Mean change in BCVA was -0.12 ± 0.19 LogMAR. Improvement and worsening of BCVA was found in 10 (52.6%) and 2 eyes (10.5%), respectively. Improvement of >2 lines in BCVA was found in 5 eyes (26.3%), and no eye lost >2 lines of BCVA. Improvement in BCVA was statistically significantly correlated with decrease in CST ($P = 0.003$).

No complication associated with STB injection including scleral perforation, infection or limitation in ocular movements was observed.

Discussion

Although intravitreal injection is the most frequently used method of anti-VEGF application in ophthalmology, alternative routes have been evaluated. Several studies reported successful application of topical and subconjunctival bevacizumab for corneal neovascularization.¹³⁻¹⁵ Kim et al.¹⁶ reported that bevacizumab penetrated into the anterior chamber of the rabbits after a single subconjunctival injection of 2.5 mg of bevacizumab. Nomoto et al.¹⁷ evaluated the pharmacokinetics of bevacizumab in rabbit eyes and showed a maximum concentration of 1418.7 and 295.8 ng/g in the iris/ciliary body and retina/choroid, respectively, after subconjunctival injection of 1.25 mg of bevacizumab. They showed that the bevacizumab level in the retina/choroid and iris/ciliary body was maintained above half-maximum inhibitory concentration for 8.6 and 8.4 weeks, respectively. Moreover, they found longer half-life for bevacizumab in the iris/ciliary body and retina/choroid after subconjunctival injection compared with those after intravitreal injection. They proposed that this may be secondary to the sustained bevacizumab delivery into the intraocular tissues due to the scleral depot binding of bevacizumab to the scleral matrix. Ryoo et al.¹⁸ reported three eyes with neovascular glaucoma

whose iris or angle neovascularization regressed remarkably after subconjunctival bevacizumab injection. Recently, Liang et al.¹¹ evaluated the effect of STB injection for the treatment of 9 eyes with myopic CNV. All nine eyes were injected with 12.5 mg of STB with repeated injections after 2 weeks for some cases. They reported complete absorption of subretinal fluid in 8 eyes.

Previous studies have reported a significant decrease in macular thickness in the untreated fellow eye after intravitreal administration of anti-VEGF agents.^{19,20} A small but effective part of the drug may escape into the systemic circulation and reach the retina via retinal vessels. This may be considered as an alternative explanation for the effect of the sub-tenon's bevacizumab injection.

Our study showed a non-significant reduction of $13.1 \pm 61.5 \mu\text{m}$ in mean CST after STB injections. Similarly, previous studies have reported a non-significant decrease in macular thickness after macular photocoagulation with or without sub-tenon's injection of triamcinolone acetonide in eyes with CSME.^{21–23} We found significant improvement in BCVA, though, one month after STB injection. Mean improvement in BCVA was 0.12 ± 0.19 LogMAR and improvement of >2 lines of BCVA was found in 26.3%. This is apparently superior to the visual acuity response after macular photocoagulation with or without sub-tenon's injection of triamcinolone acetonide as well as natural course of CSME.^{21–24} Soheilian et al.²² reported a mean change of -0.18 ± 0.19 , -0.11 ± 0.21 and 0.06 ± 0.19 LogMAR, 6 weeks after intravitreal bevacizumab, intravitreal triamcinolone acetonide and macular photocoagulation, respectively. They found improvement of >2 lines in 27.9%, 26.3%, and 5.1%, respectively.

We found a significant improvement in BCVA despite non-significant reduction in CST. Previous studies have shown that the correlation between BCVA and retinal thickness measurements is not always significant and the morphologic characteristics of the retina including integrity of outer layers, the presence of subretinal fluid and the shape of cystoid spaces are more important determinants.^{25–27} Alternatively, small sample size may explain non-significant reduction in CST in our study.

Our study has several limitations. The sample size is small. The follow up was short. We did not measure the level of the vitreous and anterior chamber VEGF. Also, this is a non-comparative study without a matched control group. Despite these limitations, this is the first study suggesting a possible role for STB injection in CSME. Intravitreal injection of anti-VEGF agents may be associated with specific complications related to the injections, including endophthalmitis, intraocular inflammation and trauma to the lens. The repeated need for injections increases the risk of adverse events. Moreover, many surgeons believe that the injections should be performed in the operating room. Although the effect of STB injection on the retinal thickness seems to be lower than intravitreal injection, it may serve as a safe alternative for intravitreal injection of bevacizumab in a subset of patients who are not feeling comfortable with intravitreal injections. Moreover, higher doses of STB may have an effect comparable to intravitreal injection. Further controlled studies are needed to elucidate the results of this study. The pharmacokinetics of the bevacizumab after subconjunctival injection has been previously described.¹⁷ Considering

anatomical differences between rabbits and humans, additional studies are required to show the pharmacokinetics of the drug after sub-tenon's injection.

Financial Interest

None of the authors have any financial interest in the subject matter of this paper.

Conflict of interest

The authors declared that there is no conflict of interest.

References

- Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology* 1984;**91**(12):1464–74.
- Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;**103**:1796–806.
- Scott IU, Danis RP, Bressler SB, Bressler NM, Browning DJ, Qin H. Diabetic Retinopathy Clinical Research Network. Effect of focal/grid photocoagulation on visual acuity and retinal thickening in eyes with non-center-involved diabetic macular edema. *Retina* 2009;**29**(8):613–7.
- Falavarjani KG, Khoshamadi A, Nilforushan N. Peripapillary nerve fiber layer thickness changes after macular photocoagulation for clinically significant diabetic macular edema. *Saudi J Ophthalmol* 2015;**29**:67–70.
- Virgili G, Parravano M, Menchini F, Brunetti M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. *Cochrane Database Syst Rev* 2012;**12**:CD007419.
- Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, et al. Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. *Ophthalmology* 2012;**119**(10):2179–88.
- Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)* 2013;**27**(7):787–94.
- Raghava S, Hammond M, Kompella UB. Periocular routes for retinal drug delivery. *Exp Opin Drug Deliv* 2004;**1**(1):99–114.
- Yalcinbayir O, Geliskan O, Kaderli B, Avci R. Intravitreal versus sub-tenon posterior triamcinolone injection in bilateral diffuse diabetic macular edema. *Ophthalmologica* 2011;**225**(4):222–7.
- Unoki N, Nishijima K, Kita M, Suzuma K, Watanabe D, Oh H, et al. Randomised controlled trial of posterior sub-Tenon triamcinolone as adjunct to panretinal photocoagulation for treatment of diabetic retinopathy. *Br J Ophthalmol* 2009;**93**(6):765–70.
- Liang IC, Chang YY, Lee TS, Lin YR, Liu KR. Treatment of myopic choroidal neovascularization with posterior sub-Tenon's bevacizumab injection (Avastin®). *Int Ophthalmol* 2014;**34**(4):971–7.
- Leung CK, Cheung CY, Weinreb RN, et al. Comparison of macular thickness measurements between time domain and spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2008;**49**:4893–7.
- DeStafeno JJ, Kim T. Topical bevacizumab therapy for corneal neovascularization. *Arch Ophthalmol* 2007;**125**(6):834–6.
- Erdurmus M, Totan Y. Subconjunctival bevacizumab for corneal neovascularization. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**(10):1577–9.
- Foroutan A, Fariba B, Pejman B, Mahmoud J, Khalil GF, Arash EA, et al. Perilimbal bevacizumab injection for interface neovascularization after deep anterior lamellar keratoplasty. *Cornea* 2010;**29**(11):1268–72.
- Kim MJ, Han ES, Kim J, Kim TW. Aqueous humor concentration of bevacizumab after subconjunctival injection in rabbit. *J Ocul Pharmacol Ther* 2010;**26**(1):49–53.

17. Nomoto H, Shiraga F, Kuno N, Kimura E, Fujii S, Shinomiya K, et al. Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits. *Invest Ophthalmol Vis Sci* 2009;**50**(10):4807–13.
18. Ryoo NK, Lee EJ, Kim TW. Regression of iris neovascularization after subconjunctival injection of bevacizumab. *Korean J Ophthalmol* 2013;**27**(4):299–303.
19. Bakbak B, Ozturk BT, Gonul S, et al. Comparison of the effect of unilateral intravitreal bevacizumab and ranibizumab injection on diabetic macular edema of the fellow eye. *J Ocul Pharmacol Ther* 2013;**29**(8):728–32.
20. Wu Z, Sadda SR. Effects on the contralateral eye after intravitreal bevacizumab and ranibizumab injections: a case report. *Ann Acad Med Singapore* 2008;**37**(7):591–3.
21. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;**30**(10):1638–45.
22. Soheilian M, Ramezani A, Bijanzadeh B, Yaseri M, Ahmadi H, Dehghan MH, et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;**27**(9):1187–95.
23. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, Beck R, Aiello LP, Antoszyk A, Bressler N, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology* 2007;**114**(6):1190–6.
24. Kwon SI, Baek SU, Park IW. Comparison of natural course, intravitreal triamcinolone and macular laser photocoagulation for treatment of mild diabetic macular edema. *Int J Med Sci* 2013;**10**(3):243–9.
25. Nunes S, Pereira I, Santos A, Bernardes R, Cunha-Vaz J. Central retinal thickness measured with HD-OCT shows a weak correlation with visual acuity in eyes with CSME. *Br J Ophthalmol* 2010;**94**(9):1201–4.
26. Otani T, Yamaguchi Y, Kishi S. Correlation between visual acuity and foveal microstructural changes in diabetic macular edema. *Retina* 2010;**30**(5):774–80.
27. Murakami T, Nishijima K, Sakamoto A, et al. Association of pathomorphology, photoreceptor status, and retinal thickness with visual acuity in diabetic retinopathy. *Am J Ophthalmol* 2011;**151**(2):310–7.